

ATTACHMENT 1

STATEMENT OF WORK

Title: Preparation of Developing Brain Tissue from Rhesus macaque for Gene Expression Analysis

I. Background Information and Overall Project Objectives

The NIH Neuroscience Blueprint Institutes and Centers (ICs), (<http://neuroscienceblueprint.nih.gov/>) share an interest in understanding normal nervous system developmental processes, as well as how abnormal developmental trajectories may affect physical and emotional health across the lifespan. There is an identified need for knowledge of detailed localization of gene expression in the developing human nervous system, with the long-term goal being to obtain detailed and searchable maps of gene expression in human brain. However, given the size and complexity of the human nervous system, straightforward adoption of available techniques is both premature and cost-prohibitive.

A tractable, near-term alternative would be to initiate pilot studies in specific brain regions/circuits in developing nonhuman primate brain, such that accumulated data would be represented in a digital brain atlas with associated informatics tools to facilitate data searches and analyses. The recent sequencing of the genome of the Rhesus macaque, *Macaca mulatta*, as well as its broad application as a research model, suggest that this nonhuman primate species would provide the optimal translational bridge between existing gene expression atlases in other species, including mouse, and future efforts in human. Ideally, these pilot studies will have a unique and significant impact on our knowledge of primate brain development and stimulate further efforts to contribute to the long term goal of a detailed Rhesus macaque digital atlas.

II. Research Objectives

The NIH Neuroscience Blueprint Institutes and Centers (ICs) has approved a “project” with the goal of generating a searchable, digital brain atlas in the macaque brain that details gene expression patterns in specific brain regions through various stages of development, from pre-natal to adult. The documentation of specific gene expression profiles through various stages of development will contribute to our knowledge of their roles in nervous system functions. This is an area of increasing interest to the neuroscience research community. It is expected that the work accomplished in the proposed project will greatly complement ongoing gene mapping efforts and determination of gene expression patterns in the nervous systems of human and other mammalian systems.

NIMH will be the lead Institute for this project, which will be separated into two inter-related contracts:

1) Preparation of Developing Brain Tissue from Rhesus macaque for Gene Expression Analysis (this contract)

Critical to the first stages of this developmental gene expression map of the Rhesus macaque is obtaining precisely dissected and appropriately prepared brain tissue from non-human primates raised in naturalistic, free-ranging colonies.

This contract will be issued to a qualified institution to provide defined regions of brain tissue specimens from animals at several developmental stages, prepared for in situ hybridization and standard Nissl staining; it will provide high quality, fresh-frozen, fixed tissue of known origin to the second contract (below) for processing.

2) High-throughput Collection of Gene Expression Data in Developing Rhesus Macaque Brain

This other contract (not the subject of this solicitation) will focus on the characterization of gene expression patterns in five specific brain regions across several developmental stages and the construction of a searchable, digital brain atlas that would be available to the public. The precise spatio-temporal expression of genes during development is critical for determining the structure and function of the brain. The determination of the profile of genes expressed in various brain regions during defined pre and post pubertal developmental stages will provide valuable information that will contribute to a greater understanding of nervous system function and the improved diagnosis, treatment, and eventual prevention of serious mental disorders.

III. Work to be Performed

This contractor will be the sole supplier of brain samples to a separate to-be-named contractor for processing, and will be required to work effectively and closely with the other facility.

The Government Project Officer (GPO) whose position is defined in Section G of the contract, shall monitor all work under the contract. Independently, and not as an agent of the Government, the Contractor shall furnish all necessary facilities, labor, services, equipment, materials and supplies (except as otherwise specified herein) to perform this contract work.

The Contractor shall use state-of-the-art methodologies and protocols to achieve all of the following requirements:

Requirement 1. Animals

Provide access to nursery-reared Rhesus macaques from free ranging colonies raised in outdoor corrals that are at least ½ acre in size, and housed in naturalistic group settings that allow for normal social interactions. Provide a full complement of veterinary staff and services to ensure compliance with NIH and DHHS policies on the care and use of animals in research. The offeror must have a currently approved DHHS Animal Welfare Assurance on file. IACUC approval will be needed for this project prior to the award of the contract. Live non-human primates will be humanely sacrificed under approved IACUC protocols and their brain tissue removed for processing.

Requirement 2. Recordkeeping

Keep accurate and secure records on each animal regarding the exact date of birth, paternal lineage (including genotype) and hierarchical status.

Requirement 3. Facility and Personnel

Provide an appropriate facility to do this work, and experienced personnel with expertise in: (a) Rhesus macaque neuroanatomy; (b) animal brain tissue extraction; (c) expertise in the dissection and blocking of tissue from specific brain regions in Rhesus macaques; and (d) expertise in the preparation of tissue for in situ hybridization analysis and Nissl staining.

Requirement 4. Prepare tissue samples

From humanly sacrificed animals, isolate and prepare high-quality brain tissue blocks from five brain regions (medial prefrontal cortex, amygdala, hippocampus, ventral striatum, and primary visual cortex) for in situ hybridization and Nissl staining for the purpose of generating a gene expression map of the developing Rhesus macaque brain (Note: in situ, Nissl staining, and creation of the gene expression map will be done by a separate contractor). Tissue blocks from the above 5 brain regions shall be prepared from four (4) animals (2 female, 2 male) at each of five (5) defined developmental time points (birth, 3 months, 1 year, 2 years, and 6 years) for a total of 20 animals.

Requirement 5. Packaging and shipping

In accordance with all local, state and federal regulations, package and ship brain sections to a to-be-named facility for in situ, Nissl staining, and creation of the gene expression map. The remainder of the brains shall be appropriately blocked and cryopreserved for shipment to and storage at a central tissue bank located at the NIH for use in the future.

For the required shipping/distribution of biological materials the Contractor shall:

- (a) Have all appropriate licenses for shipping and distribution of biohazardous material.
- (b) Have appropriate and documented protocols for shipping brain tissue to outside facilities.
- (c) Transfer tissue samples to the to-be-named Contractor, as directed by the GPO, under the terms and conditions of an approved "Material Transfer Agreement," (to be approved by the GPO prior to shipments - see attached sample).
- (d) Notify other facility, and the Project Officer, prior to the shipment of the tissue samples.
- (e) Ship specified brain regions under this contract to the to-be-named contractor within two weeks of dissection.
- (f) Store remaining brain tissue in fresh frozen state for potential use, if options are exercised.
- (g) As directed by the Project Officer, by the end of this contract transfer to the NIH (or to a designated third party) all data and unused brain tissue collected. These materials are the sole property of the U.S. Government.

Requirement 6. Reporting requirements

The Contractor shall provide written summaries of the work performed under the contract after the end of each contract quarter and each contract year.

These reports shall include, as a minimum, the following:

Quarterly Reports

- (a) Complete description of each brain region harvested, including the stereotaxic coordinates of the target region and size of the tissue block.
- (b) The age and sex of the animal from which the tissue was harvested.
- (c) Complete records of housing conditions, parental lineage, paternal genotype, and date of birth for each animal from which tissue was harvested.
- (d) A narrative summary of the work performed during the reporting period, including a discussion of any significant problems which have affected (or might continue to affect) contract performance and proposed corrective action; a discussion of work to be performed during the next reporting period.

Annual Reports

A brief annual report shall be compiled to summarize the information contained in that year's quarterly reports.

Final Report

A final report, including an executive summary of no more than three pages, shall summarize all of the activities conducted under this contract.

IV. Options

1) Option to Extend the Term of the Contract:

This contract consists of a two-year base period that may be followed by two, one-year options.

- OPTION 01 Contract year 3
- OPTION 02 Contract year 4

If exercised by the Government, each option year following the two-year base contract period will require the Contractor to continue work on requirements 1-3, as outlined above, based upon the needs of the Government. These options may be exercised if all of the animals were not available within the first two years of the contract, if there were significant delays in harvesting the required tissue, or if additional work is required (see below).

2) Option for Additional Quantities

As progress is made in gene mapping efforts in mammalian model organisms and new approaches and methodologies are developed, the needs and focus of this contract may expand to accommodate the mapping of additional genes in more brain regions.

If this option is exercised by the Government, the Contractor shall:

- OPTION 03: prepare up to 3 additional brain regions at the same developmental stages. The Project Officer shall approve the additional brain regions for the work during any option periods. No new animals will be needed under this option.

[NOTE 1 TO THE OFFEROR: FOR THE PURPOSES OF PREPARING A COST PROPOSAL, ASSUME 3 ADDITIONAL BRAIN REGIONS WILL BE PREPARED FROM THE ORIGINAL 20 SACRIFICED ANIMALS; PROVIDE A TOTAL COST, AND A COST PER BRAIN REGION]

- OPTION 04: prepare originally specified brain region tissue from 1-3 additional developmental stages (ages). The Project Officer shall approve the additional development stages. This option will require 4 - 12 additional animals.

[NOTE 2 TO THE OFFEROR: FOR THE PURPOSES OF PREPARING A COST PROPOSAL, ASSUME 12 ADDITIONAL ANIMALS WILL BE REQUIRED, 2 MALE AND 2 FEMALE EACH, AT AGES: PRE-NATAL, 6 MONTHS, AND 4 YEARS; PROVIDE TOTAL COSTS AND COSTS PER ANIMAL FOR THE TOTAL POSSIBLE 12 ANIMALS].